Diabetic ketoacidosis (DKA) is one of the most common causes of severe metabolic illness that results in prolonged hospitalization of dogs and cats. Prompt diagnosis and appropriate therapy are essential for a good outcome for these patients. DKA cases can be some of the most rewarding critical care patients to treat, as the prognosis is often good as long as the complicating disease processes are not too severe. This lecture will cover the pathophysiology of DKA, fluid and insulin therapy, as well as the acid/base and electrolyte abnormalities seen in DKA patients, and how to treat these derangements.

Pathophysiology
DKA is characterized by hyperglycemia, metabolic acidosis, and ketosis. For the development of DKA, both a complete or relative insulin deficiency must be present along with increased levels of the diabetogenic hormones, including glucagon, epinephrine, norepinephrine, cortisol, and growth hormone. If both of these requirements are not met, DKA will not occur.

Insulin is released in the normal patient in response to increased serum glucose concentrations. Insulin has multiple effects on the liver; it stimulates glycogen synthesis, enhances uptake of glucose from the portal blood, and inhibits gluconeogenesis and glycogenolysis. Insulin also stimulates muscle cells to move glucose intracellularly, inhibits proteolysis, and stimulates protein synthesis. In addition, insulin stimulates adipose tissue to increase movement of glucose and lipoprotein intracellularly. Simultaneously, it stimulates lipogenesis and inhibits lipolysis. Insulin deficiency results in hyperglycemia, increased lipolysis, increased delivery of glycerol and free fatty acids (FFA) to the liver, and increased proteolysis resulting in increased amino acids for gluconeogenesis.

Glucagon directly opposes the effects of insulin. It stimulates glucose production in the liver by increasing gluconeogenesis and glycolysis. It also increases production of ketones by the liver. The catecholamines, epinephrine and norepinephrine, increase gluconeogenesis and glycogenolysis by the liver as well as stimulate lipolysis, which provides the FFA needed for production of ketones. Cortisol and growth hormone decrease glucose uptake and utilization and increase gluconeogenesis in the liver, worsening the hyperglycemia. The catecholamines and cortisol may be elevated by concurrent disease or medications that the cats have received.

FFA are released from adipose tissue and can be used as an oxidative energy source as well as be metabolized into ketones in the liver. Within the liver, FFA can be esterified into triglycerides, can be metabolized to CO2 and water via the tricarboxylic cycle, or can be converted into ketone bodies. When they are used to make ketones, FFA are converted into coenzyme A derivative acyl-CoA. This is oxidized to acetyl-CoA, which reacts with acetoacetyl-CoA to form ß-hydroxy-ß-methylglutaryl-CoA. This molecule can then be split to form acetoacetate and acetyl-CoA. Acetoacetate, in the presence of NADH, is reduced to ß-hydroxybutyrate. Acetone can be formed by spontaneous decarboxylation of acetoacetate. Acetoacetate and ß-hydroxybutyrate are organic acids (acetone has a neutral charge). Normally, the ketones acetoacetate and ß-hydroxybutyrate are used as an energy source in tissues through out the body via the tricarboxylic cycle. Acetone can be eliminated via the lungs or converted to glucose. All three ketone bodies can be eliminated in the urine. In DKA, the rate of ketone production vastly overwhelms the body’s ability to metabolize the ketones, resulting in ketosis and a metabolic acidosis with an increased anion gap.

Hyperglycemia and ketonemia cause an osmotic diuresis that can lead to significant dehydration, electrolyte depletion, and even hypovolemia and cardiovascular shock. The metabolic acidosis can cause respiratory fatigue from attempts at respiratory compensation and cardiovascular collapse through decreased cardiac contractility, arrhythmias, and vasodilation. Hyperosmolality can also develop with sometimes severe consequences for the CNS. Initial treatment of these patients needs to be aimed at correcting the fluid, acid-base, and electrolyte disturbances as these tend to be more life-threatening than the hyperglycemia.

Common Concurrent Disease Processes
Common disease processes in cats presenting with DKA include hepatic lipidosis, pancreatitis, chronic renal failure, hyperthyroidism, inflammatory bowel disease, and bacterial infection as well as administration of exogenous corticosteroids. In dogs, hyperadrenocorticism, pancreatitis, hypothyroidism, renal disease, urinary tract infections, otitis, and neoplasia are common concurrent disease processes. Also, in intact female dogs, diestrus results in increased growth hormone levels, and typically will cause DKA every time the diabetic dog has a heat cycle.
Fluid Therapy

Patients that present with DKA are often dehydrated and hypovolemic at the same time. Fluid therapy must be aimed at treating both the volume depletion and dehydration while addressing the ongoing losses that occur. Increased losses are primarily due to polyuria from the osmotic diuresis but also can be from vomiting, diarrhea, or other losses. Choice of a replacement solution to use in the DKA patient is often debated, with 0.9% NaCl often recommended. Normal saline is recommended because many of these patients present hypovolemic and hyponatremic. The hyponatremia is often a pseudo-hyponatremia secondary to the hyperglycemia and ketonemia. For every 100 mg/dl increase in glucose, the Na⁺ concentration will decrease by 1.6 mEq/L. This is due to the water that is held in the intravascular space by the glucose. Often once the patient has had the hyperglycemia corrected, the Na⁺ concentration is normal, or even elevated. Hypernatremia can occur because of the excessive water loss that occurs from the osmotic diuresis created by the glucosuria and ketonuria. For these reasons, as well as the acidifying nature of 0.9% NaCl, any of the balanced, isotonic electrolyte solutions (LRS, Norm-R, Plasmalyte) may be preferred.

Fluid rates should be determined by assessment of the patient. If cardiovascular compromise is detected, a shock bolus (45-60 ml/kg) or part of a shock bolus is indicated. More commonly, severe dehydration is detected, and an estimate of the percentage of dehydration can be made based on physical exam parameters. The formula: dehydration + maintenance + ongoing losses = fluid rate can be used. Dehydration = % dehydration x body weight (kg) x 1000ml/kg, and should be replaced over 6-12 hours. Maintenance = 2-4 ml/kg/hr. Ongoing losses must be measured or estimated and replaced over the following 2-4 hour period.

Insulin Therapy

Insulin therapy is essential in the treatment of the DKA patient for several reasons. It normalizes serum glucose, inhibits lipolysis and the release of FFA, increases glycogenesis and decreases glycogenolysis, allows ketones to be utilized, decreases hepatic FFA oxidation to form ketones, and increases hepatic FFA esterification to form triglycerides.

Insulin therapy should be instituted once the patient has been stabilized cardiovascularly. This usually requires a few hours of fluid therapy, and waiting until the patient has been stabilized results in fewer cases of hypotension secondary to water shifting from the intravascular space (as the glucose concentration in the blood decreases) to the intracellular space (as glucose moves intracellularly). It has been shown that human DKA patients have no detrimental effect when insulin therapy is delayed up to 17 hours post presentation. Delaying insulin therapy will also allow for electrolyte abnormalities such as hypokalemia to be addressed, as insulin therapy will only worsen them. Only regular crystalline insulin should be administered to these patients in the emergency stabilization. This can be accomplished either by administering it intramuscularly or as a constant rate infusion. Regular insulin can be administered IM at a dose of 0.2 units/kg initially, followed by 0.1 units/kg every hour. This is continued until the glucose concentration reaches 300 mg/dl or lower, then regular insulin can be given IM at 0.25-0.5 units/kg every 4-6 hours. Regular insulin should not initially be administered SQ in these patients due to their dehydration and therefore unreliable absorption from the SQ tissues. It can be switched over to SQ dosing once the hydration status has been corrected, and may require every 6-8 hour dosing. For the extremely sick DKA, CRI is preferable as it allows for more precise regulation of the glucose as well as administration of larger amounts of insulin, which is essential for resolution of the ketosis. A constant rate infusion can be made at a dose of 1.1 units/kg/day for cats and 2.2 units/kg/day for dogs. This is made by placing the insulin dose in a 240 ml bag of normal saline, and starting the infusion at 10 ml/hr. A chart is made to adjust the rate of insulin CRI based on the patient’s blood glucose level. Dextrose is added to the fluids if the patient’s blood glucose drops below a certain level. Administration of both insulin and dextrose containing fluids allow for maximal insulin doses to be given, which is necessary for correction of the metabolic acidosis.

<table>
<thead>
<tr>
<th>Blood glucose</th>
<th>Insulin rate</th>
<th>% Dextrose in fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;250</td>
<td>10ml/hr</td>
<td>none</td>
</tr>
<tr>
<td>200-250</td>
<td>7ml/hr</td>
<td>none</td>
</tr>
<tr>
<td>150-199</td>
<td>5ml/hr</td>
<td>2.5%</td>
</tr>
<tr>
<td>100-149</td>
<td>3ml/hr</td>
<td>5%</td>
</tr>
<tr>
<td>&lt;100</td>
<td>none</td>
<td>5%</td>
</tr>
</tbody>
</table>

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The chart can be adjusted as needed to provide the individual patient with the desired glycemic control and to try to reduce the number of times the fluids need to be changed.

The goal for reduction of serum glucose is to not drop the glucose by more than 50-100 mg/dl/hr. This is to prevent a sudden reduction in serum osmolality, which can result in cerebral edema and neurologic signs. Chronic hyperosmolality causes production of idiogenic osmoles within the brain. These intracellular solutes help preserve intracellular volume within the CNS in the presence of an increased serum osmolality. Rapid decreases in the serum osmolality can result in fluid shifting intracellularly, as the cells cannot get rid of the osmoles immediately. A slower reduction in serum osmolality allows for removal of the idiogenic osmoles and equilibration of intracellular and serum osmolality. The patient’s mentation should be monitored closely, and if a decline in mentation is noted as the glucose is dropped rapidly, treatment with mannitol at 0.25-0.5 gm/kg IV over 20-30 minutes is indicated.

Regular insulin is used until the patient is no longer ketotic and is eating (or being fed enterally) its full energy requirements. Then the patient can be switched over to long-acting insulin SQ every 12 hours.

**Acid-Base**

These patients may present with a severe metabolic acidosis. The acidosis is primarily from the ketosis, but if the patient’s perfusion is severely affected by the water loss, a lactic acidosis may also be present. Measurement of the pH by venous blood gas analysis is extremely helpful in managing these cases. Fluid therapy, especially if using one of the balanced electrolyte solutions that have a neutral pH (such as LRS, Norm-R, or Plasmalyte) will usually improve the pH through dilution. Also, if poor perfusion is present, fluid therapy should resolve the lactic acidosis and improve the pH. Sodium bicarbonate therapy may be needed in some cats with DKA but they remain in the minority. These include patients that are cardiovascularly unstable secondary to their acidosis, usually with pH < 7.1. It has been shown in humans that bicarbonate therapy has not changed morbidity, mortality, or length of hospital stay, but there is an increased likelihood of a metabolic alkalosis as the body metabolizes the ketones over the next few days. Insulin therapy, a mainstay of treatment for diabetes, provides the best means of addressing the metabolic acidosis. As ketogenesis is halted, and as ketones are metabolized back into FFA, HCO₃⁻ is released and the pH will be corrected. If Na HCO₃ therapy is warranted, the following formula is used to calculate the amount to be given: Base deficit x 0.3 x body weight (kg) = bicarbonate deficit. Usually, 1/4 to 1/3 of the calculated deficit is given over several hours.

**Sodium**

Dogs and cats presenting with DKA may be hyponatremic due to the hyperglycemia or hypernatremic secondary to free water loss from the osmotic diuresis. They may even have a normal sodium concentration due to both of these factors. On presentation, hyponatremia is the most common. Careful monitoring of the Na⁺ concentration several times a day is indicated as dramatic changes can occur once fluid and insulin therapy have been initiated. In hyponatremic patients, treatment for the hyperglycemia can result in fluid shifting from the intravascular space into the dehydrated intracellular space, causing a rapid rise in serum Na⁺ concentration. Some of these patients will require changing their fluids from an isotonic solution to a hypotonic solution such as 0.45 % NaCl to prevent severe hypernatremia.

**Potassium**

Patients presenting with DKA usually have profound total body K⁺ depletion secondary to the osmotic diuresis, loss into the GI tract with vomiting or diarrhea, and decreased intake from inappetence to anorexia. Their serum K⁺ concentration may not reflect the severity of K⁺ depletion because of shifting of K⁺ out of the intracellular space secondary to the acidosis. With an acidosis, H⁺ ions move intracellularly to be buffered, and in order to maintain electroneutrality in the cells, K⁺ ions move out. Hypokalemia is associated with skeletal, gastrointestinal, and myocardial muscle weakness. It may be associated with ECG changes including a flattened T-wave, elevated P wave, increased R wave amplitude, and a depressed S-T segment. Hypokalemia is also associated with mental dullness.

Once the patient has been started on insulin therapy, K⁺ will move intracellularly again. This will occur as it is co-transported along with glucose and also as the metabolic acidosis is corrected and H⁺ move back out of the cell. Early, aggressive therapy with KCl is indicated, even in patients with normal to slightly low K⁺ concentrations. Supplementation with Kmax (0.5 mEq/kg/hr) is sometimes not sufficient in these patients, and can be exceeded with careful monitoring including a continuous ECG.
Phosphorous

Hypophosphatemia is relatively common in patients with DKA. Phosphorus depletion results from the osmotic diuresis, decreased intake due to anorexia, and reduced renal tubular reabsorption secondary to the acidosis. Phosphorus shifts extracellularly with acidosis similar to K+. This allows for serum phosphorus concentrations to be normal in many patients despite severe total body depletion. On presentation, the patient’s phosphorous concentration may be low, normal, or even high if pre-renal azotemia is present. Hypophosphatemia has been reported in about 40% of cats at presentation, with many more developing hypophosphatemia during hospitalization and treatment if appropriate monitoring and supplementation is not provided. Dogs are also at risk for development of hypophosphatemia and should be monitored appropriately.

Treatment with insulin and correction of the metabolic acidosis will result in intracellular shifting of phosphorus and a rapid decrease in the serum concentration. Severe hypophosphatemia (<1.5 mg/dl) may result in hemolysis, particularly in cats. Dogs appear to be slightly more tolerant of hypophosphatemia, and hemolysis is usually not seen until concentrations are less than 1.0 mg/dl. In humans, this is believed to be due to a lack of energy substrate for the Na+/K+ ATPase pump, resulting in intracellular accumulation of Na+ and therefore water, cell swelling, and eventually lysis. The mechanism for hemolysis in dogs and cats is less well understood, but may include this mechanism as well as increased Heinz body formation that is often also seen in cats with DKA. Other signs of hypophosphatemia include muscle weakness, tremors, hypotension, and ataxia.

Hypophosphatemia at levels < 2.0 mg/dl should be treated with a CRI of potassium phosphate (K phos) at a dose of 0.03-0.06 mEq/kg/hr. Severe cases of hypophosphatemia (< 1.0 mg/dl) may require doses as high as 0.12-0.2 mEq/kg/hr. Phosphorous concentrations should be rechecked after 6-12 hours of therapy. An alternative way to supplement phosphorous is to provide half the K+ requirements as KCl and the other half as K phos.

Magnesium

Hypomagnesemia is also common in patients with DKA. It results from the osmotic diuresis causing increased losses as well as decreased intake from anorexia. Often called the forgotten ion, magnesium is essential to the activity of many enzymes. It is a cofactor for ATPase, so is essential for the operation of many of the cell pumps, including K+ uptake into the cells. Hypomagnesemia is often associated with severe, refractory hypokalemia, which is impossible to correct until the magnesium has been normalized. Other signs of hypomagnesemia include muscle tremors, muscle weakness, arrhythmias, CNS depression, and seizures. Total magnesium concentrations of less than 1.5 mg/dl should be treated with a magnesium sulfate CRI of 0.5-1.0 mEq/kg/24 hours.

Switching to Long Acting Insulin

Once the patient’s volume status, electrolytes, and acid-base abnormalities have been stabilized, it is time to consider switching to long acting insulin. If a patient requires total parenteral nutrition (TPN), the CRI of insulin should be continued until TPN is no longer required. Due to its high dextrose concentration, TPN will likely cause the patient to remain hyperglycemic. Switching from the CRI to long acting insulin is best accomplished once the patient is receiving full resting energy requirement (RER) enterally, either by voluntarily eating or tube feedings. In preparation of starting long acting insulin, the CRI should be discontinued about 1 hour prior to administration of SQ insulin, and the patient should be fed a meal.

Prognosis

The majority of patients that present with DKA, even the sickest, can be treated and go on to have an excellent quality of life providing they receive the necessary, intensive care. Obviously, this disease process requires dedicated owners that are willing to treat their pets appropriately and seek frequent veterinary care as needed. Additionally, the underlying disease process that has resulted in development of the DKA state can also affect prognosis, especially if it is a non-treatable or non-curable condition.

References


